Mathematical Model of Cronic Meyloid Leukemia

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Present Challenges of Mathematics in Oncology and Biology of Cancer

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Main Talk

1. Cronic Meyloid Leukemia
   - What is stem cell
   - Characteristic features
   - Hematopoiesis
   - The Philadelphia chromosome

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   - What is stem cell
   - Characteristic features
   - Hematopoiesis
   - The Philadelphia chromosome
2. Model (1)
   - Steady state
   - Local stability and bifurcation
   - Concept of $\mathcal{R}_0$
   - Analysis at $\mathcal{R}_0 = 1$
   - Global stability

Main Talk

What is stem cell

stem cell is

- young,
- primitive and unspecialized cell with remarkable potential to renew,
- differentiate and develop into any desired tissue or organ of the body.

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In conclusion: it is young cells having infinite self renewing capacity and potential for differentiation

Main Talk

Characteristic features

- Self renewal: Unlimited proliferative potential.
- Differentiation: Differentiate into various cell types

  Totipotency,

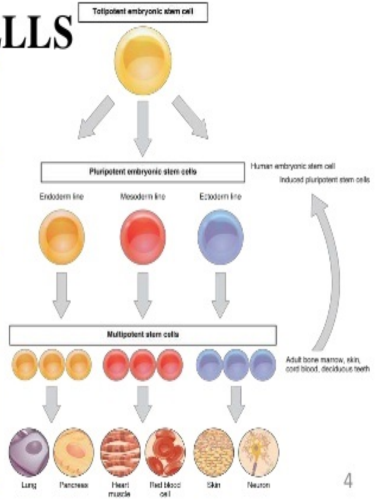
  Pluripotency,

  Multipotency.
- Regeneration potential: A means of repair.

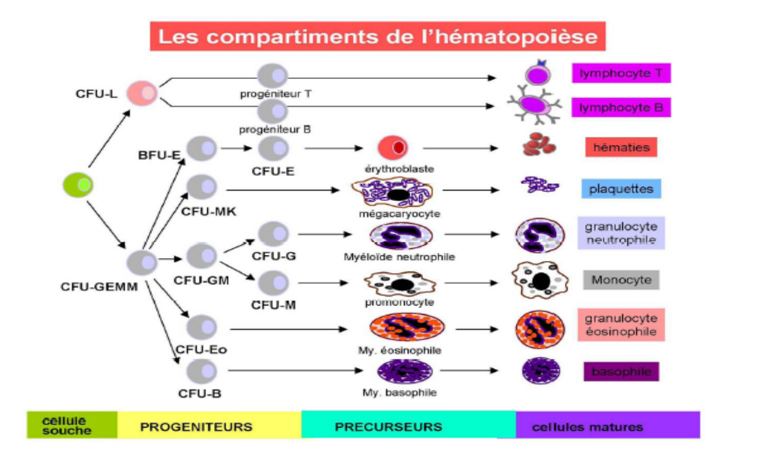
Type of stem cells

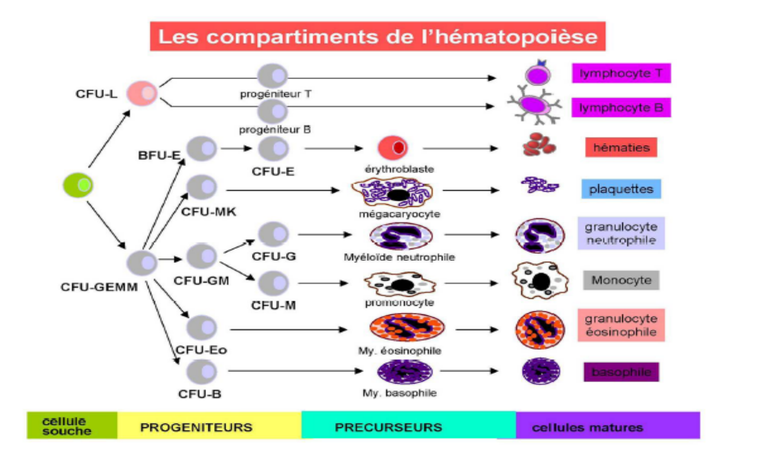
TYPES OF STEM CELLS

Type of stem cell	What it can be	Examples
Totipotent cells	Each cell can develop into a new individual	Cells of embryo of 1-3 days
Pluripotent cells	Each cell can form any cell type (over 200)	Cells of blastocyst 5-14 days
Multipotent cells	Cells differentiate and can form a number of tissue types.	Fetal tissue, cord blood, adult cells



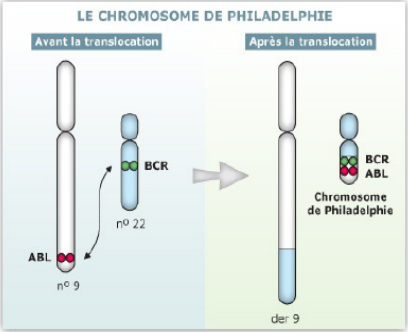
Main Talk

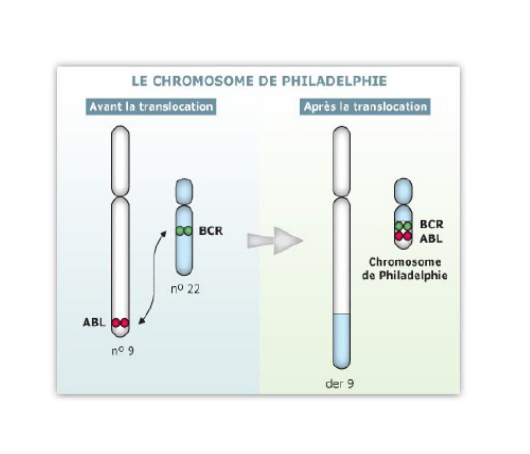

Les compartiments de l'hématopoïèse
CFU-L
progéniteur T
progéniteur B
lymphocyte T
lymphocyte B
BFU-E
CFU-E
érythroblaste
hématies
CFU-MK
mégacaryocyte
plaquettes
CFU-G
Myéloïde neutrophile
granulocyte neutrophile
CFU-GEMM
CFU-GM
CFU-M
promonocyte
Monocyte
CFU-Eo
My. éosinophile
granulocyte éosinophile
CFU-B
My. basophile
basophile
cellule souche
PROGENITEURS
PRECURSEURS
cellules matures



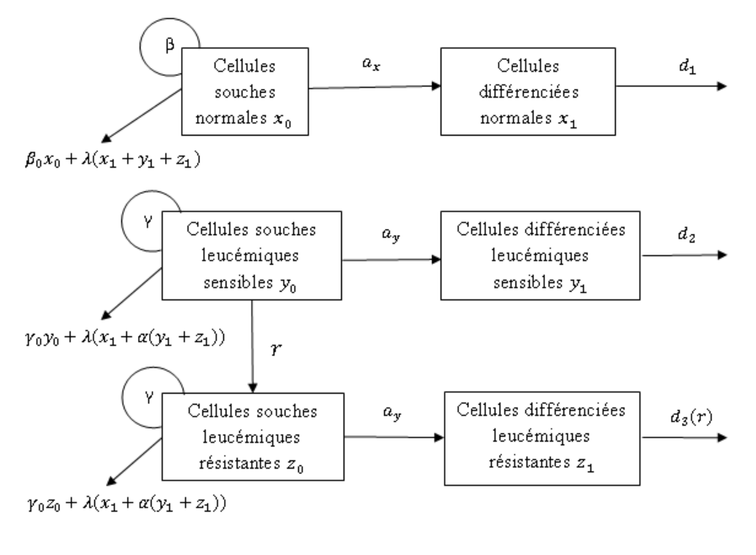
- Hematopoiesis is the set of phenomena which contribute to the production of blood cells.

Main Talk


LE CHROMOSOME DE PHILADELPHIE
Avant la translocation
Après la translocation
BCR
ABL
nº 22
nº 9
BCR
ABL
Chromosome
de Philadelphie
der 9



Chronic myeloid leukemia is a disease characterized by a chromosomal abnormality acquired (called Philadelphia chromosome).


β
Cellules souches normales x_0
a_x
Cellules différenciées normales x_1
d_1
$\beta_0 x_0 + \lambda(x_1 + y_1 + z_1)$
γ
Cellules souches leucémiques sensibles y_0
a_y
Cellules différenciées leucémiques sensibles y_1
d_2
$\gamma_0 y_0 + \lambda(x_1 + \alpha(y_1 + z_1))$
r
γ
Cellules souches leucémiques résistantes z_0
a_y
Cellules différenciées leucémiques résistantes z_1
$d_3(r)$
$\gamma_0 z_0 + \lambda(x_1 + \alpha(y_1 + z_1))$

Model (1)

(1)
$$\begin{cases} \dot{x}_0 = (\beta - a_x - \beta_0 x_0 - \lambda(x_1 + y_1 + z_1))x_0, \\ \dot{x}_1 = a_x x_0 - d_1 x_1, \\ \dot{y}_0 = (\gamma - a_y - \gamma_0 y_0 - \lambda(x_1 + \alpha y_1 + \alpha z_1))y_0 - r y_0, \\ \dot{y}_1 = a_y y_0 - d_2 y_1, \\ \dot{z}_0 = (\gamma - a_y - \gamma_0 z_0 - \lambda(x_1 + \alpha y_1 + \alpha z_1))z_0 + r y_0, \\ \dot{z}_1 = a_y z_0 - d_3(r) z_1, \end{cases}$$

where

(2)
$$a_x < a_y,$$

(3)
$$a_y + r < \gamma,$$

(4)
$$a_x < \beta,$$

(5)
$$d_3(r) \leq d_2,$$

$d_3(r) \searrow$ on r and $d_3(0) = d_2$.

Symbols and definitions of populations

subpopulations	definitions
x_0	normal stem cells
x_1	normal differentiated cells
y_0	leukemic sensitive stem cells
y_1	leukemic sensitive differentiated cells
z_0	leukemic resistant stem cells
z_1	leukemic resistant differentiated cells

Table: Symbols and definitions of populations.

Symbols and definitions of parameters.

parameters	definitions
β_0	death rate of the normal stem cells
γ_0	death rate of leukemic stem cells
β	division rate of normal stem cells
γ	division rate leukemic stem cells
λ	competitive parameter of the stem and progenitor cells
a_x	produce rate of the normal stem cells
a_y	produce rate of the leukemic stem cells
d_1	death rates of the normal progenitors cells
d_2	death rates of the leukemic progenitors cells
$d_3(r)$	death rates of the normal leukemic progenitors cells
r	resistant parameter
α	$0 < \alpha < 1$

Table: Symbols and definitions of parameters.

Analysis of case $r = 0$: without resistant population.

(6)
$$\begin{cases} \dot{x}_0 = (\beta - a_x - \beta_0 x_0 - \lambda(x_1 + y_1))x_0, \\ \dot{x}_1 = a_x x_0 - d_1 x_1, \\ \dot{y}_0 = (\gamma - a_y - \gamma_0 y_0 - \lambda(x_1 + \alpha y_1))y_0, \\ \dot{y}_1 = a_y y_0 - d_2 y_1. \end{cases}$$

Let $q = \frac{\gamma - a_y}{\beta - a_x}$, $d_1^* = \frac{\lambda a_x}{\beta_0}\left(\frac{1-q}{q}\right)$ and $d_2^* = \frac{\lambda a_y}{\gamma_0}(q - \alpha)$.

Denote

RI: $d_1 < d_1^*$ and $d_2 > d_2^*$,

RII: $d_1 > d_1^*$ and $d_2 < d_2^*$,

$RIII$: $d_1 > d_1^*$ and $d_2 > d_2^*$,

RIV: $d_1 < d_1^*$ and $d_2 < d_2^*$.

Main Talk

equilibrium	name	expression
$E_0 = \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \end{pmatrix}\right)$	trivial equilibrium	
$E_1 = \left(\begin{pmatrix} \xi_1 \\ \frac{a_x}{d_1}\xi_1 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \end{pmatrix}\right)$	disease free equilibrium	$\xi_1 = \dfrac{(\beta - a_x)d_1}{\beta_0 d_1 + \lambda a_x}$
$E_2 = \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \eta_2 \\ \frac{a_y}{d_2}\eta_2 \end{pmatrix}\right)$	healthy free equilibrium	$\eta_2 = \dfrac{(\gamma - a_y)d_2}{\gamma_0 d_2 + \lambda\alpha a_y}$
$E_3 = \left(\begin{pmatrix} \xi_3 \\ \frac{a_x}{d_1}\xi_3 \end{pmatrix}, \begin{pmatrix} \eta_3 \\ \frac{a_y}{d_2}\eta_3 \end{pmatrix}\right)$	endemic equilibrium	$\xi_3 = \dfrac{\xi_1 - \frac{\lambda a_y d_1}{(\beta_0 d_1 + \lambda a_x)d_2}\eta_2}{1 - \frac{\lambda a_x \lambda a_y}{(\gamma_0 d_2 + \lambda\alpha a_y)(\beta_0 d_1 + \lambda a_x)}}$ $\eta_3 = \dfrac{\eta_2 - \frac{\lambda a_x d_2}{(\gamma_0 d_2 + \lambda\alpha a_y)d_1}\xi_1}{1 - \frac{\lambda a_x \lambda a_y}{(\gamma_0 d_2 + \lambda\alpha a_y)(\beta_0 d_1 + \lambda a_x)}}$

Table: Equilibrium formulation.

Main Talk

Theorem

Let $\lambda \geq 0$, and assume that the conditions $(1) - (5)$ are satisfied. Then

1. E_0 *is unstable.*
2. *If* $q < 1$ *and* $d_1 < d_1^*$*, then* E_1 *is locally asymptotically stable. Else,* E_1 *is unstable.*
3. *If* $q > \alpha$, $d_2 < d_2^*$*, then* E_2 *is locally asymptotically stable. Else,* E_2 *is unstable.*
4. *If* $\alpha > \alpha^* = \frac{\lambda a_x}{\beta_0 d_1 + \lambda a_x} - \frac{\gamma_0 d_2}{\lambda a_y}$, $d_1 > d_1^*$ *and* $d_2 > d_2^*$*, then* E_3 *is locally asymptotically stable. Else,* E_3 *is unstable.*

Case 1: $q \leq \alpha$		Case 1: $\alpha < q < 1$		Case 3: $1 \leq q$	
region	stability	region	stability	region	stability
RI	E_0 is unstable E_1 is L.A.S. E_2 is unstable	RI	E_0 is unstable E_1 is L.A.S. E_2 is unstable	RI disappear	
RII disappear		RII	E_0 is unstable E_1 is unstable E_2 is L.A.S.	RII	E_0 is unstable E_1 is unstable E_2 is L.A.S.
RIII	E_0 is unstable E_1 is unstable E_2 is unstable E_3 is L.A.S.	RIII	E_0 is unstable E_1 is unstable E_2 is unstable E_3 is L.A.S.	RIII	E_0 is unstable E_1 is unstable E_2 is unstable E_3 is L.A.S.
RIV disappear		RIV	E_0 is unstable E_1 is L.A.S. E_2 is L.A.S.	RIV disappear	

Table: Summary of the model with $r = 0$ and $\alpha > \alpha^*$

Case 1: $q \leq \alpha$		Case 1: $\alpha < q < 1$		Case 3: $1 \leq q$	
region	stability	region	stability	region	stability
RI	E_0 is unstable E_1 is L.A.S. E_2 is unstable	RI	E_0 is unstable E_1 is L.A.S. E_2 is unstable	RI disappear	
RII disappear		RII	E_0 is unstable E_1 is unstable E_2 is L.A.S.	RII	E_0 is unstable E_1 is unstable E_2 is L.A.S.
RIII	E_0 is unstable E_1 is unstable E_2 is unstable	RIII	E_0 is unstable E_1 is unstable E_2 is unstable E_3 is unstable	RIII	E_0 is unstable E_1 is unstable E_2 is unstable
RIV disappear		RIV	E_0 is unstable E_1 is L.A.S. E_2 is L.A.S. E_3 is unstable	RIV disappear	

Table: Summary of the model with $r = 0$ and $\alpha < \alpha^*$

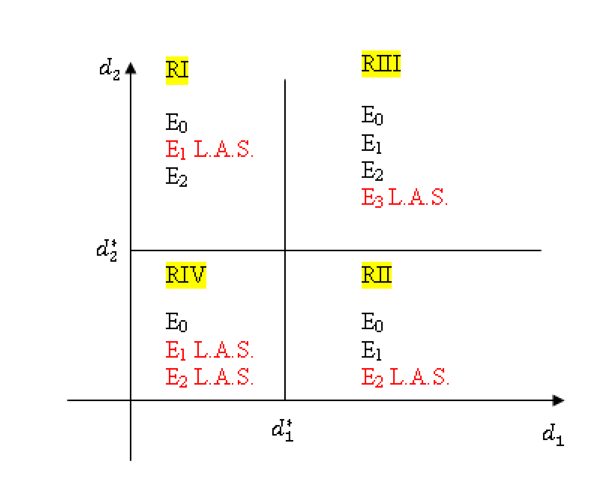


Figure: Bifurcation diagram for model when $\alpha < q < 1$.

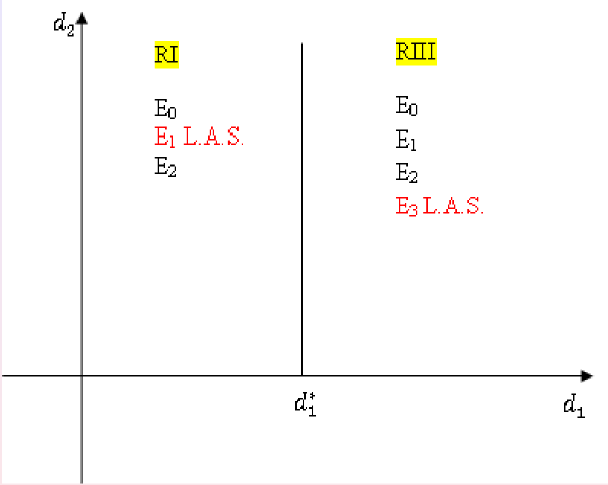


Figure: Bifurcation diagram for model when $q \leq \alpha$.

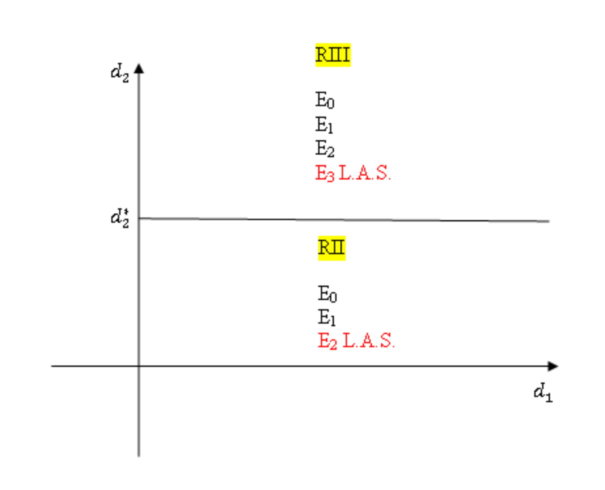


Figure: Bifurcation diagram for model when $q > 1$.

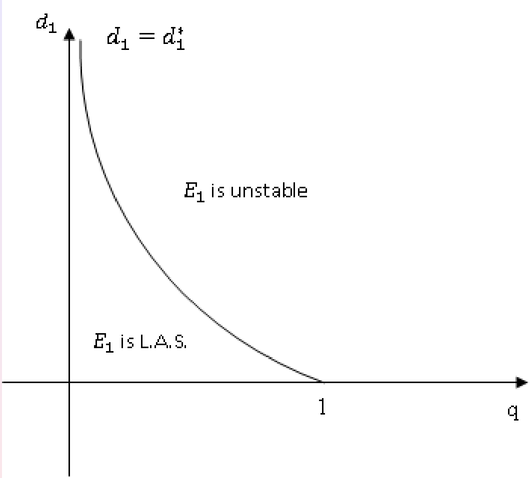


Figure: Bifurcation diagram for DFE.

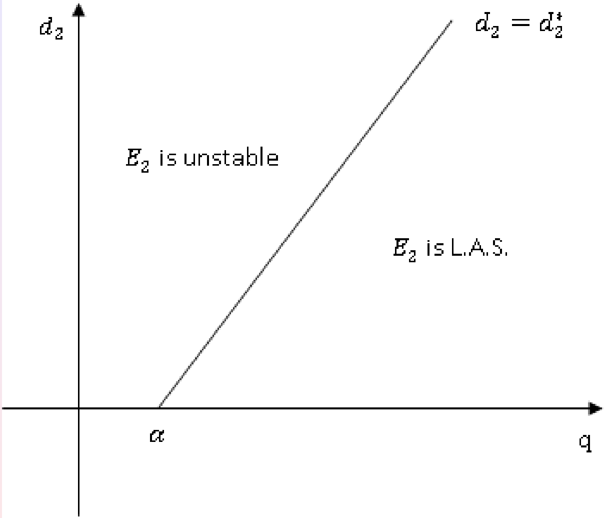


Figure: Bifurcation diagram for HFE.

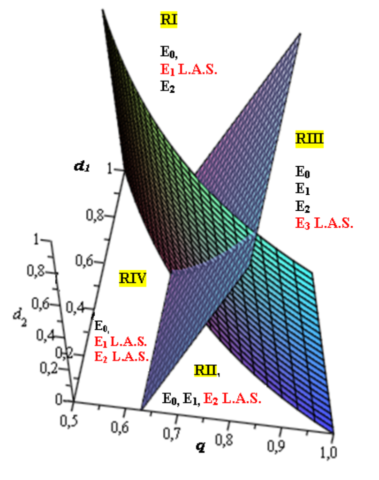


Figure: Bifurcation diagram for model.

Main Talk

The disease free equilibrium (DFE) for this nondimensionalized general model of chronic myeloid leukemia may be used to find the basic reproduction number $\mathcal{R}_0$, which indicates the average number of new infections. The basic epidemiological reproductive number is given by

$$\mathcal{R}_0 = \frac{\gamma}{\frac{(\beta - a_x)\lambda a_x}{\beta_0 d_1 + \lambda a_x} + a_y}. \tag{7}$$

However, this nondimensional number is not enough to characterize the dynamics of model (1)-(5).

Main Talk

Theorem

Let $d_2' = \frac{\lambda a_y}{\gamma_0}\left(\frac{\lambda a_x}{\beta_0 d_1 + \lambda a_x} - \alpha\right)$ *and* $d_1' = \frac{\lambda a_x}{\beta_0}\left(\frac{1-\alpha}{\alpha}\right)$.

1. *If* $d_2' < d_2 < d_2^*$, *the unique endemic equilibrium disappears whenever* $\mathcal{R}_0 > 1$ *and is close to* 1.
2. *If* $d_2 > d_2^* > d_2'$, *the unique endemic equilibrium is locally asymptotically stable whenever* $\mathcal{R}_0 > 1$ *and is close to* 1.
3. *If* $d_2 < d_2'$ *and* $d_1 < d_1'$, *the unique endemic equilibrium disappears whenever* $\mathcal{R}_0 > 1$ *and is close to* 1.

Main Talk

Using the following Lyapunov functions V_i according the Lasalle theorem, we can show the global asymptotic stability of E_i $(i = 1, 2, 3)$, where

1. $V_1 = \left(x_0 - \xi_1 - \xi_1 \ln \frac{x_0}{\xi_1}\right) + \frac{\lambda}{2a_x}\left(x_1 - \frac{a_x}{d_1}\xi_1\right)^2 + y_0 + \frac{\lambda\alpha}{2a_y}y_1^2.$
2. $V_2 = x_0 + \frac{\lambda}{2a_x}x_1^2 + \left(y_0 - \eta_2 - \eta_2 \ln \frac{y_0}{\eta_2}\right) + \frac{\lambda\alpha}{2a_y}\left(y_1 - \frac{a_y}{d_2}\eta_2\right)^2.$
3. $V_3 = \left(x_0 - \xi_3 - \xi_3 \ln \frac{x_0}{\xi_3}\right) + \frac{\lambda}{2a_x}\left(x_1 - \frac{a_x}{d_1}\xi_3\right)^2 + \left(y_0 - \eta_3 - \eta_3 \ln \frac{y_0}{\eta_3}\right) + \frac{\lambda\alpha}{2a_y}\left(y_1 - \frac{a_y}{d_2}\eta_3\right)^2.$

Global stability

Denote $q_1 = \frac{4\gamma_0}{\beta_0+4\gamma_0}$, $q_2 = \frac{\gamma_0+4\alpha^2\beta_0}{4\alpha\beta_0}$, $d_1^\bullet = \frac{1}{4}\frac{\lambda a_x}{\gamma_0}$ and $d_2^\bullet = \frac{1}{4\alpha}\frac{\lambda a_y}{\beta_0}$.

Theorem

1. *If* $q < q_1$, $d_1^\bullet < d_1 \leq d_1^*$ *and* $d_2 > d_2^\bullet$, *then* E_1 *is globally asymptotically stable in* $\mathbb{R}_+^4 / \{0\} \times \mathbb{R}_+^3$.
2. *If* $q > q_2$, $d_1 > d_1^\bullet$ *and* $d_2^\bullet < d_2 \leq d_2^*$, *then* E_2 *is globally asymptotically stable in* $\mathbb{R}_+^4 / \mathbb{R}_+^2 \times \{0\} \times \mathbb{R}_+$.
3. *If* $d_1 > \max(d_1^*, d_1^\bullet)$ *and* $d_2 > \max(d_2^*, d_2^\bullet)$, *then* E_3 *is globally asymptotically stable in* $\mathbb{R}_+^4 / \{0\} \times \mathbb{R}_+^3 \bigcup \mathbb{R}_+^2 \times \{0\} \times \mathbb{R}_+$.

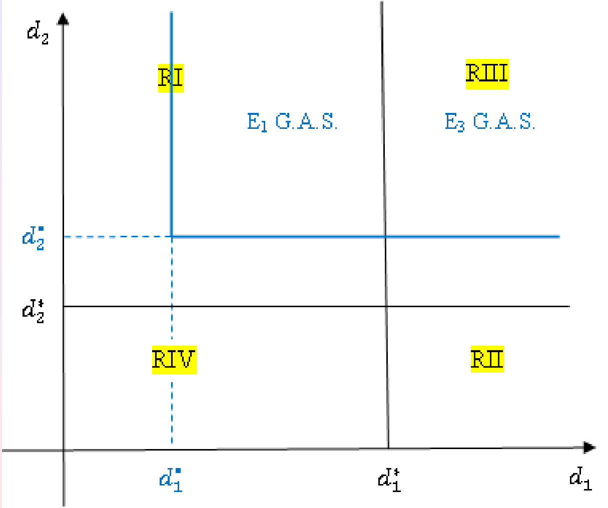


Figure: Global stability diagram for model when $q < q_1$.

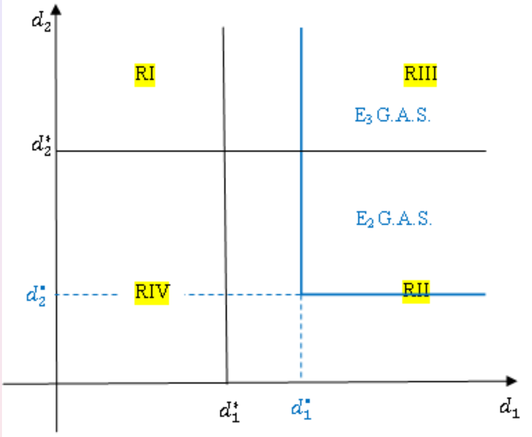


Figure: Global stability diagram for model when $q > q_2$.

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Thank you for your attention.